REMARKS

In a communication from the Patent Office dated July 2, 2004, the Office indicated that Applicants April 29, 2004 amendment did not include the text of the withdrawn claims and did not properly show changes relative to previous versions of paragraphs. Applicants have corrected the issues noted by the Office and include the arguments and comments set forth in the April 29, 2004 amendment..

Claims 1-17 were pending. Claims 3-8 have been withdrawn as directed to a non-elected invention. Claims 1, 10, 11, and 14-17 have been amended. No new matter has been entered.

Oath/Declaration

The Office alleges that the declaration is defective for failing to provide post office addresses. Applicants note that an executed declaration that provided the post office addresses was filed on May 11, 2004.

Objections

The specification is objected to for allegedly citing the incorrect statute in paragraph [0001]. Applicants have replaced paragraph [0001] accordingly, rendering the objection moot. Applicants respectfully request the withdrawal of the objection.

Rejections under 35 U.S.C. § 112

Claims 16 and 17 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. According to the Office the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office further alleges that the specification

> does not provide a written description of a transgenic mouse expressing hyperphosphorylated human tau protein as recited in claim 16 nor a transgenic mouse expressing human tau protein forming filamentous aggregates as

> recited in claim 17. In the absence of a clear written description of the mice to be used in the screening assays, the written description requirement is not satisfied for the claimed methods of screening.

(Office Action, pages 3-4).

The standard for determining compliance with the Written Description requirement of section 112 is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. See, *e.g.*, *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). Further, it is established law that limitations appearing in claims need not be literally recited in the specification. The issue is not whether words used in the claims are present in the specification but, rather, whether the ***concept*** expressed by the words is present. *In re Anderson*, 176 U.S.P.Q. 331 (C.C.P.A. 1973) (emphasis added).

One of skill in the art would have known that Applicants were in possession of the claimed methods at the time the application was filed. Applicants specifically generated and tested transgenic mice expressing different forms of human tau demonstrating that Applicants were in possession of the claimed invention. The specification teaches that overexpressing tau results in hyperphosphorylation based on the studies of other transgenic animals. The specification states, "An increase in tau phosphorylation at sites associated with Alzheimer's disease pathogenesis is seen..." (Specification, p. 2, ¶ [0006], as filed). The specification also discusses the role of tau hyperphosphorylation in tau pathologies and the use of the hyperphosphorylation of tau (*i.e.* detecting, blocking, or inducing) in models of neurodegenerative diseases (see, for example, p. 10, ¶ [0038]). The specification also describes tau pathologies involving filamentous aggregates and viewing them in mice using various antibodies (see, for example, p. 10). The specification clearly describes methods using mice either containing hyperphosphorylated tau or filamentous aggregates to identify drugs that either block hyperphosphorylation or block the formation of filamentous aggregates.

Therefore, even though Applicants did not specifically demonstrate that the mice described in the Examples are hyperphosphorylated or form filamentous aggregates, the "concept" of the claims is clearly expressed throughout the specification. One of ordinary skill in the art would readily accept that Applicants were in possession of the

claimed invention at the time of filing. Accordingly, Applicants' specification complies with the written description requirement of 35 U.S.C. § 112, first paragraph.

Claims 1, 2, and 9-17 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in such a way as to enable one skilled in the art to make and/or use the invention. The Office alleges that the "specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice, because the phenotype of a transgenic animal cannot be predicted." (Office Action, page 4). The Office further alleges that creating a transgenic mouse is unpredictable and would require undue experimentation. Applicants respectfully disagree.

The crux of the Office's argument is that predicting the phenotype of a transgenic mouse cannot be predicted until the mouse is made and therefore, without an actual reduction to practice the present invention is not enabled. The Office cites Wall (Wall R.J., *Theriogenology* (1996) 45:57-68, hereinafter "Wall") and Sigmund (Sigmund C.D., *Arterioscler Thromb Vasc Biol* (2000) 20:1425-1429, hereinafter "Sigmund") as proof that the production of transgenic mice is unpredictable. However, Applicants respectfully assert that the references have either been misinterpreted or not applicable to present invention.

As an initial matter, the present invention is clearly enabled by the specification because Applicants describe in the instant application the generation of transgenic mice.

Wall discusses transgenic "Livestock: progress and prospects for the future." Wall discusses transgene integration efficiency and how insertion point of the transgene in the genome can effect the function of the transgene. However, Wall does not state that generating a transgenic animal would require undue experimentation or be burdensome. Rather, at most, Wall suggests that more than one animal with the transgene needs to be generated to obtain an animal with the desired transgene and phenotype. The experimentation that is required to identify such animals is not undue. Even though a large amount of experimentation may be required, the types of experiments are routine for the skilled artisan. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question

provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (M.P.E.P. § 2164.06).

The present application provides a ***reasonable amount*** of guidance with respect to the direction in which the experimentation should proceed. The present specification describes the types of transgenic vectors and how to make transgenic mice. Other methodologies to create transgenic mice are routinely performed by the skilled artisan and cannot be considered undue. Even complex or time-consuming experiments are not necessarily undue. "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (M.P.E.P. § 2164.01). Such is the present case. Wall concludes, "The tools for gene transfer are in hand, albeit the process is inefficient." (Wall, page 64). Thus, Wall does not state that experimentation to create transgenic mice is an undue burden. Furthermore, the main focus of Wall is on the creation of transgenic farm animals. Therefore, most of the comments cited by Wall are not relevant to mice since the creation of transgenic mice is routine in the art.

Sigmund discusses "Are studies in Genetically altered mice out of control?" Sigmund is similar to Wall in that Sigmund does not state that one cannot generate a transgenic mouse of one's choosing, but rather that it may require the generation of more than one mouse before the desired phenotype is created. Again, Sigmund does not state that undue experimentation is required to identify such phenotypes. At most, Sigmund suggests that the identification of specific phenotypes requires the generation of more transgenic mice. However, as discussed above and in the present specification, the creation of transgenic mice is routine in the art. The Office is again reminded that a large amount of experimentation is not undue if the types of experiments performed are routine.

Therefore, since the generation of transgenic mice is routine and nothing more than routine experimentation would be required to generate the transgenic mice described in the pending claims, the present invention is enabled.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 10-13 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that claims 10-13 are indefinite in their recitations of "5' flanking sequence" and "the initial noncoding portion of the second PrP exon" because the metes and bound of these regions are not clearly set forth. Applicants respectfully disagree.

Applicants describe in Example 1 the preparation of transgenic vectors (see, pages 11-13). In Example 1, Applicants also describe the cloning and sub-cloning steps in producing a vector that comprises the "5' flanking sequence" and the "initial noncoding portion of the second PrP exon". Applicants have also amended claim 10 to recite "5' flanking sequence of said prion gene promoter" so that the claim is even clearer. One of skill in the art understands that a "5' flanking sequence" is the part of the sequence of a gene that is before the first exon and does not including any coding sequence. One of skill in the art would be able to determine what this region is based on the sequence of the prion gene as well as through the methods that are described in the specification to create the transgenic vectors. The same is true for the "initial, noncoding region of the second PrP exon." One of skill in the art would know that this refers to the region of the second exon that does not code for any of the prion gene product. The boundaries of which are also defined by the methods described in Example 1 of the specification.

Furthermore, Applicants explicitly describe the PrP promoter and PrP exons that are included in the vector in Table 3. Accordingly, claims 10-13 are definite.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Zehr *et al.* (October 1999, Society for Neuroscience Abstracts 25(1):447.1, hereinafter "Zehr"). The Office alleges that Zehr discloses the production and characterization of transgenic mice expressing human Tau polypeptides and that the expression of the tau gene was "driven by the mouse prion promoter...Thus, the claimed invention is disclosed in the prior art." (Office Action, page 7). Applicants disagree.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ishihara *et al* (October 1999, Society for Neuroscience Abstracts 25(1):447.2, hereinafter "Ishihara1"). The Office alleges that Ishihara1 discusses the production and characterization of transgenic mice expressing human tau polypeptides, wherein the tau cDNA expression is driven by a mouse prion protein promoter and "thus, the claimed invention is disclosed in the prior art." (Office Action, page 8). Applicants disagree.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ishihara *et al.* (*Neuron* (1999) 24:751-762, hereinafter "Ishihara2"). The Office alleges that Ishihara2 discusses the production and characterization of transgenic mice expressing human tau polypeptides, wherein the tau cDNA expression is driven by a mouse prion protein promoter and "thus, the claimed invention is disclosed in the prior art." (Office Action, page 9). Applicants disagree.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,475,723 (hereinafter "'723 patent"). The Office alleges that the '723 patent discusses transgenic mammals expressing the Tau polypeptide and that "the reference teaches that the prion gene promoter should be used...Thus the claimed invention is disclosed in the prior art." (Office Action, page 9). Applicants disagree.

Claims 1, 2, and 9-13 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,664,443 (hereinafter "'443 patent"). The Office alleges that the '443 patent discusses transgenic mice expressing the human Tau polypeptide under the control of the mouse prion promoter and "thus, the claimed invention is disclosed in the prior art." (Office action, page 10). Applicants disagree.

Applicants respectfully assert that the claims as amended are not anticipated by any of the references cited by the Office.

For a reference to anticipate a claim, each and every element as set forth in the claim must be found either expressly or inherently described in a single prior art reference. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

As amended claim 1 recites:

> A transgenic mouse, comprising a transgene, said transgene comprising a polynucleotide encoding a human tau protein operably linked to at least a portion of a regulatory region of a mouse prion gene, wherein said regulatory region comprises a promoter of said prion gene, a 5' flanking sequence of said prion gene promoter and the first PrP exon, wherein said transgenic mouse expresses human tau protein.

None of the references cited by the Office discuss or even suggest a transgenic mouse where the polynucleotide encoding a human tau protein is operably linked to a regulatory region of mouse prion gene that comprises the prion gene promoter and 5' flanking sequence of the prion gene promoter, and the first PrP exon. At most the references suggest using the prion promoter to drive the expression of the tau transgene. However, none of the references discuss or suggest using the first PrP exon. Therefore, none of the references contain each and every element of the pending claims. Accordingly, the pending claims are novel.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 14-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ishihara1 or Ishihara2. The Office alleges that either reference discusses the production and characterization of transgenic mice expressing human Tau polypeptide and that

> Given the phenotype of the disclosed transgenic mice and further given that said phenotype correlates with a pathological hallmark of a number of neurodegenerative diseases, it would have been obvious to use the mice to screen for drugs that may be useful in treating a neurodegenerative disease. Moreover, given the observed hyperphosphorylated tau protein in the brain and spinal cord of the transgenic mice, the skilled artisan would have been motivated to use the mice to screen for drugs that block this pathological process...Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

(Office Action, page 11). Applicants respectfully disagree.

As is clear from MPEP §2143, in order to provide a *prima facie* case of obviousness, the Examiner must first establish motivation to combine or modify the references.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2143. The Examiner cannot rely upon a reasonable expectation of success alone to establish motivation. Such reliance is improper.

Neither the Ishihara1 nor the Ishihara2 reference discuss or even suggest a transgenic mouse as described in pending claim 1. There is no motivation within the references either explicitly or implicitly that would have impelled one of ordinary skill in the art to make the transgenic mouse as it is recited in the claims. Therefore, one of skill in the art would not have been motivated to screen a mouse as described in claim 1. Without the motivation to make the mouse that is described in the pending claims the references fail to "teach or suggest all the claim limitations" of the pending claims.

Therefore, since the references fail to provide motivation to use a mouse as described in the pending claims and also do not teach or even suggest all the claim limitations, the present invention is not *prima facie* obvious.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

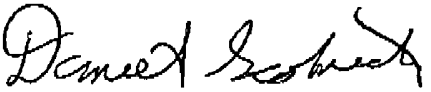
Docket No.: PHRM0031-100 (6225)
Serial No. 09/767,088

PATENT
Filed: January 22, 2001

Conclusion

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6928 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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